REMARKS

Claims 18 and 25-35 are pending in the application. Claims 1-17 and 19-24 were previously canceled. Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender (U.S. Patent No. 4,336,185, hereafter "Niswender") in view of Wedeking et al. (U.S. Patent No. 6,093,382; hereafter "Wedeking") and Sinkule et al. (European Patent Application No. 0282057; hereafter "Sinkule"). Claims 18, 25-28, and 30-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Goldenberg (U.S. Patent No. 5,698,178; hereafter "Goldenberg"). Claims 18, 25-28, and 31-35 are further rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent No. 6,740,304. Applicants address each of these rejections as follows.

Rejections Under 35 U.S.C. § 103(a)

Claims 18 and 25-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Sinkule. Claims 18, 25-28, and 30-35 are also rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Goldenberg. As the basis for the first obviousness rejection, the Office states that Niswender teaches "folic acid and salts, esters, and amides thereof and an antibody, such as a gamma globulin...and/or radionuclide or radionuclides" (Office Action, pg. 3); Wedeking teaches "gadolinium-folate (folic acid) conjugates that are used to target the radionuclide to tumor cells" (Office Action, pg. 3); and Sinkule teaches a conjugate containing three components: "1) a monoclonal antibody..., 2) a radionuclide, and 3) a chemotherapeutic agent, such as folate or analogs thereof" (Office Action, pg. 4) and disclose use of "IgG, such as 443A6 which recognize a 40k dalton epithelial antigen found on human breast adenocarcinomas" (Office Action, pg. 5). The Office further states that it would have been obvious to a skilled artisan to substitute the antibodies of Sinkule for those of Niswender, substitute variants of folic acid, and "utilize the

conjugates of the combined disclosure...of Wedeking et al. and Sinkule et al. for targeting a gadolinium-folate (folic acid)-antibody conjugate to a cell" (Office Action, pg. 5). Applicants respectfully disagree with the basis for this rejection.

Legal Standard for Obviousness in View of KSR v. Teleflex

The Supreme Court in KSR International Co. v. Teleflex (127 S. Ct. 1727, 1739; 82 USPQ2d 1385 (2007)), stated:

> The combination of familiar elements according to known methods is likely to be obvious when it does not more than yield predictable results.

In addition, the Court states:

> [W]hen a patent "simply arranges the old elements with each performing the same function it has been known to perform" and yields no more than one would expect from such an arrangment, the combination is obvious. (127 S. Ct. at 1740).

The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 In View of the Supreme Court Decision in KSR International Co. v. Teleflex Inc. (Federal Register Vol. 72, No. 195, page 57527) further states:

> When considering obviousness of a combination of known elements, the operative question is thus "whether the improvement is more than the predictable use of prior art elements according to their established functions. (Emphasis added).

The pending claims are directed to conjugates, which contain two different targeting molecules: an antibody, antibody fragment, or antibody construct with affinity for a *tumor-associated* antigen and a *non-toxic* folate. Applicants submit that, as explained below, the claimed invention is *more than* the predictable use of prior art elements, and, therefore, *nonobvious* in view of the cited references.

The claims are directed to conjugates that contain *two different* targeting moieties: an antibody, antibody fragment, or antibody construct with affinity for a *tumor-associated* antigen, and a *non-toxic* folate. None of Niswender, Wedeking, and Sinkule teaches or suggests the use of two different targeting moieties in a single conjugate molecule.

Niswender describes conjugates that contain a folic acid moiety conjugated to a stabilizing protein radical (e.g., rabbit gamma globulin). Neither the folic acid moiety nor the stabilizing protein radical in the Niswender conjugates are described for their function in targeting a cell or binding a cell *in vivo*. Thus, Niswender clearly does not teach or suggest a combination of two different *targeting* moieties.

Wedeking describes the use of folates and folic acid derivatives for cellular uptake and chemotherapy. Wedeking does not disclose a conjugate that contains both a folate or folic acid derivative *and* a tumor-specific antibody and, therefore, also fails to teach or suggest the combination of two different targeting moieties.

Sinkule teaches conjugates containing a tumor-specific antibody conjugated to a chemotherapeutic agent (e.g., a *toxic* folic acid analog). Sinkule does not suggest the replacement of the *toxic* folic acid analog with a *non-toxic* folic acid. Applicants submit that such a substitution would reduce the chemotherapeutic function of the conjugates disclosed by Sinkule. Thus, Sinkule also clearly fails to teach or suggest the combination of the two targeting moieties required by the pending claims.

Prior to the Applicants' disclosure, it was unknown to a skilled artisan whether the claimed conjugates would have efficacy *in vivo*. Applicants note that the synthesis of conjugates containing an antibody, a radionuclide, and non-toxic folic acid, due to the complexity of the conjugates, is more difficult than the synthesis of a non-toxic folic acid or folic acid analog alone. Nothing in the cited art, even if combined, suggests the efficacy of the conjugates encompassed by the present claims.

In addition, Applicants point out to the Office that the chemical formula disclosed in Niswender does not encompass or suggest the claimed conjugates. In the formula

disclosed in Niswender (column 1, lines 19-25), a carboxy radical, a protein radical (-C(=O)-NH-R^3), and a cyclic radical of formula A are alternatives for the R and R^1 positions, providing that at least one of R or R^1 is a carboxy, or a salt or amide thereof. Thus, because one group must be taken by the carboxy alternative, only one position remains, which can accommodate either a protein radical, such as gamma globulin, or a cyclic radical A, which may then be radiolabeled. This is clearly evident in the Examples in Niswender, wherein only folate-thyroglobulin, or folate-radiotyrosine are generated. Hence Niswender entirely fails to teach or suggest the conjugates encompassed by the claims.

In short, as the claimed conjugates are more difficult to make and were unknown prior to the Applicants' disclosure to mediate a biological effect *in vivo*, even if the cited references were combined as suggested by the Office, a skilled artisan would have had no reasonable expectation of success for use of the Applicants' invention prior to the Applicants' disclosure.

Moreover, the Examination Guidelines for Determining Obviousness (cited above, pg. 57529) provide the following rationales supportive for a finding of obviousness (emphasis added):

> (A) Combining prior art elements according to known methods to yield *predictable results*;
> (B) Simple substitution of one known element for another to obtain *predictable results*;
> (C) Use of known technique to improve similar devices (methods, or products) *in the same way*;
> (D) Applying a known technique to a known device (method, or product) ready for improvement to yield *predictable results*;
> (E) "Obvious to try"- choosing from a finite number of identified, predictable solutions, with a *reasonable expectation of success*;
> (F) Known work in one field of endeavor may prompt variation of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been *predictable* to one of ordinary skill in the art;

(G) Some *teaching, suggestion, or motivation* in the prior art that would have led one of ordinary skill to modify the prior art reference teachings to arrive at the claimed invention.

Applicants submit that the cited references fail to meet any of these criteria supportive for a finding of obviousness. As noted above, nothing in the cited art would lead a skilled artisan to predict the *in vivo* effect of the conjugates encompassed by the claims. Also, given the complexity and difficulty in making the claimed conjugates, one skilled in the art would not reasonably predict their effect *in vivo* prior to the Applicants' disclosure.

Further, Applicants submit that there is no teaching, suggestion, or motivation to combine Niswender, Wedeking, and Sinkule to arrive at the Applicants' claimed invention. The molecules disclosed by Niswender are radionuclide-labeled folic acids that may be conjugated to a stabilizing protein (e.g., thyroglobulin, methylated bovine serum albumin (BSA), sheep serum albumnin (SSA), rabbit gamma globulin (RGG), porcine serum albumin (PSA), and human serum albumn (HSA) (see, column 1, lines 33-37). Niswender describes the use of the radionuclide-labeled folic acids for use in *in vitro* assays (e.g., competitive binding assays) (see, column 1, lines 11-16). Wedeking discloses radionuclide-labeled folates and folic acid derivatives for use in tumor cell binding and cellular uptake (see, for example, column 1, lines 12-29). Sinkule discloses conjugates containing an antibody, a radionuclide, and a chemotherapeutic agent (e.g., folic acid analogs) for chemotherapy (see, for example, column 2, lines 23-34). The use of the molecules of Niswender (i.e., for *in vitro* assays) is different from the use of the molecules of Wedeking and Sinkule, for tumor cell binding and cellular uptake, and chemotherapy, respectively. As the disclosure of Niswender, Wedeking, and Sinkule are directed to disparate uses, which necessarily require different properties, Applicants submit that prior to the present invention, a skilled artisan would not have been motivated to combine Niswender, Wedeking, and Sinkule to arrive at the Applicants' invention.

Moreover, Applicants submit that the Office is using improper hindsight analysis to pick and choose elements from the cited references to substantiate the present obviousness rejection.

For all the reasons stated above, Applicants respectfully request that the obviousness rejection in view of Niswender, Wedeking, and Sinkule be withdrawn.

Goldenberg Does Not Cure the Deficiency of Niswender, Wedeking, and Sinkule

Claims 18, 25-28, and 30-35 are rejected under 35 U.S.C. § 103(a) as obvious over Niswender in view of Wedeking and Goldenberg. As the basis for this second obviousness rejection, the Office has replaced Sinkule with Goldenberg. The Office relies on Goldenberg for teaching conjugates that contain "antibodies and at least one diagnostic or therapeutic agent" and include "radionuclides...and cancer chemotherapeutic drugs, such as folic acid analogues" (Office Action, page 7).

Goldenberg discloses immunoconjugates that contain an antibody that binds to a multidrug transporter protein, an antibody that binds to a tumor-associated antigen or infectious agent antigen, and a therapeutic or diagnostic agent. Goldenberg describes the use of folic acid analogs (i.e., *toxic* folic acid analogs) as chemotherapeutic agents. Goldenberg aims to target cells over-expressing P-glycoprotein (i.e., the only multidrug transporter protein disclosed) without causing intolerable side-effects by targeting both the P-glycoprotein and an antigen specific for a tumor or infective agent (see, column 3, lines 15-21, and column 4, lines 12-20). Goldenberg does not teach or suggest conjugates having: (1) an antibody, an antibody fragment, or antibody construct with affinity for a *tumor-associated* antigen, and (2) a *non-toxic* folate. Furthermore, a skilled artisan would not be motivated to substitute the *toxic* folic acid analog disclosed in Goldenberg with a *non-toxic* folic acid, as such substitution would reduce the chemotherapeutic function of

the conjugates. For these reasons, Goldenberg fails to cure the deficiency of Niswender and Wedeking (described above).

Applicants respectfully request that this basis for rejection also be withdrawn.

Rejection for Nonstatutory Obviousness-type Double Patenting

Claims 18, 25-28, and 31-35 are further rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-6 of U.S. Patent No. 6,740,304. Claims 1-6 of the '304 patent recite conjugates including a folate, a radionuclide or mixture of radionuclides, and an *inert* human IgG or IgM antibody or fragment or construct thereof. The inert human IgG and IgM antibody has considerable advantages as a carrier in providing advantageous circulation times, but does *not* provide any targeting effect.

In contrast, the antibody component of the conjugates of the present invention have a *targeting* function. The pending claims require the antibody, antibody fragment, or antibody construct to have *affinity for a tumor-associated antigen*. Given that the antibodies recited in claims 1-6 of the '304 patent are inert, these claims do not teach or suggest using antibodies, antibody fragments, or antibody constructs in a conjugate where the antibody component has *affinity* for a tumor-associated antigen.

Applicants further point out that in the prosecution of the '304 patent, the Office suggested the term "inert antibody" to indicate an antibody which does not bind to a tumor surface receptor. The Office indicates that the present claims do not exclude inert antibodies, however, because an antibody cannot both bind to a relevant target and be inert, the claims of the '304 patent and the present invention do not overlap in scope. For these reasons, Applicants submit that the nonstatutory obviousness-type double patenting rejection over claims 1-6 of the '304 patent should be withdrawn.

CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Applicants respectfully request an interview with the Examiner to resolve any remaining issues.

Enclosed is a Petition to extend the period for replying to the Office Action for three months, to and including May 27, 2008, as May 26, 2008 was a Federal holiday, and a check in payment of the required extension fee.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 27 May 2008

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